Journal of Neurology (2026) 273:52
https://doi.org/10.1007/s00415-025-13558-3

ORIGINAL COMMUNICATION

Neuromodulation in Parkinson's disease with transcranial pulse stimulation: evidence of clinical efficacy and cortical oscillatory changes

Anna Carolyna Gianlorenco[1] · Lucas Camargo[1] · Huan-Jui Yeh[2,3] · Elayne Borges Fernandes[1,4] · Joao Victor Ribeiro[1] · Dilana Hazer-Rau[5] · Rafael Storz[5] · Felipe Fregni[1]

Received: 18 November 2025 / Revised: 1 December 2025 / Accepted: 2 December 2025

Abstract

Background Parkinson's disease (PD) is a progressive neurodegenerative disorder for which current pharmacological treatments, while initially effective, often lead to long-term motor fluctuations and complications. Transcranial pulse stimulation (TPS) is a novel non-invasive neuromodulation technique that uses mechanical stimuli through shockwaves to induce neuroplasticity.

Methods This open-label, single-arm pilot study enrolled 14 individuals with PD who received 12 TPS sessions over 4 weeks. Stimulation targeted motor and symptom-specific cortical regions. Outcomes were assessed across motor, non-motor domains, and EEG at baseline, after 3, 6, 9, and 12 sessions, and at 1-month follow-up.

Results TPS produced significant and consistent improvements across different domains. After 12 TPS sessions, UPDRS total scores improved by 9.43 points ($p < 0.001$, Cohen's $d = -0.566$), and UPDRS Part III improved by 4.93 points ($p < 0.001$, $d = -0.498$). Non-motor symptom burden was reduced by 19.14 points ($p = 0.014$, $d = -0.754$). Cognitive performance improved substantially, with a 7.28-point gain on the SCOPA-COG ($p < 0.001$, $d = 1.161$). Quality of life improved by 1.30 points on the PDQ-39 SI ($p = 0.005$, $d = -0.690$), and depression symptoms by 3.43 points on the BDI-II ($p = 0.008$, $d = -0.644$). Follow-up analyses demonstrated that all clinical effects were sustained one month after treatment.

Conclusion TPS appears to induce clinically meaningful and lasting improvements across multiple domains in PD, accompanied by EEG changes that indicate enhanced neuroplasticity. However, due to the nature of this pilot open-label trial, these results should be interpreted as preliminary, hypothesis-generating findings that require confirmation in adequately sham-controlled randomized clinical trials.

Keywords Parkinson's disease · Transcranial pulse stimulation · TPS · Brain stimulation · Electroencephalogram

Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder that affects over 10 million individuals worldwide and represents a major cause of disability in aging

Anna Carolyna Gianlorenco and Lucas Camargo have contributed equally.

✉ Felipe Fregni
fregni.felipe@mgh.harvard.edu

[1] Spaulding Neuromodulation Center and Center for Clinical Research Learning, Spaulding Rehabilitation Hospital and Massachusetts General Hospital, Harvard Medical School, 1575 Cambridge Street, Cambridge, MA, USA

[2] Department of Physical Medicine and Rehabilitation, Taipei Hospital, Ministry of Health and Welfare, New Taipei City, Taiwan

[3] Institute of Public Health, National Yang Ming Chiao Tung University, Taipei, Taiwan

[4] Laboratory of Neuroscience and Neurological Rehabilitation, Physical Therapy Department, Federal University of Sao Carlos, Sao Carlos, SP, Brazil

[5] STORZ MEDICAL AG, Tägerwilen, Switzerland

Published online: 29 December 2025

populations [1]. While dopaminergic medications such as levodopa remain the cornerstone of symptom management, they are limited by diminishing efficacy over time, motor fluctuations, and the emergence of dyskinesias and non-motor complications [2, 3]. Despite decades of pharmacologic research, treatment options for PD remain suboptimal—particularly for addressing the broad spectrum of non-motor symptoms and for patients who experience motor fluctuations even on optimized therapy [4, 5]. There is thus an urgent need to develop novel, well-tolerated, non-invasive interventions that can augment existing treatments and provide durable relief across multiple symptom domains.

Neuromodulation techniques have emerging options for the treatment of neurodegenerative disorders, such as PD. Among these, deep brain stimulation (DBS) is a known approach for this population, focusing mainly on motor symptoms, e.g., tremor [6, 7], but, as an invasive method, DBS still raises concerns about the risk of cerebrovascular side effects and worsening of psychiatric symptoms [8, 9]. In contrast, non-invasive brain stimulation (NIBS) methods offer a safer profile, with a low risk of severe side effects, while still demonstrating beneficial effects in individuals with PD [10, 11]. Techniques, such as focused ultrasound, transcranial direct current stimulation, and repetitive transcranial magnetic stimulation, have been explored in this context [12]. However, the results of these studies are mixed and/or the effects are mostly limited to the motor symptoms [12–14].

Transcranial pulse stimulation (TPS) is a new form of non-invasive neuromodulation that uses repetitive, single high-pressure ultrashort shockwave pulses within the ultrasound frequency range to modulate brain activity in a targeted and focal manner [15, 16]. Unlike other neuromodulation modalities, TPS is capable of reaching deep brain structures with high spatial resolution without being affected by pathological conductivity changes [15, 16]. Clinical studies have demonstrated its safety and efficacy in Alzheimer's disease, showing improvements in cognition and functional connectivity [17–19]. The technique is now CE-approved for use in this population. More recently, a pilot work has explored the safety and feasibility of TPS in PD. A retrospective study by Osou et al. [20] in 20 patients with PD demonstrated significant improvements in motor symptoms after ten sessions of TPS, with no major side effects. Also, Manganotti et al. [21] demonstrated that only one session of active TPS was enough to induce improvements in the amplitude of resting tremor in 16 PD. It is known from other neuromodulation techniques like high-frequency DBS, that suppression of beta oscillations is associated with improved motor performance [22]. To judge the potential of TPS as an adjunctive therapy for PD and also the need for a mechanistic assessment of modifications of neural circuits and their clinical effects comprehensive, multi-domain outcome measures are used.

To address this gap, we conducted a prospective, open-label pilot study to evaluate the safety, feasibility, and preliminary efficacy of TPS in individuals with Parkinson's disease. We designed a 4-week, 12-session TPS protocol combining standardized cortical stimulation with individualized symptom-based targeting and peripheral neuromodulation [23]. Participants were assessed across motor and non-motor domains, such as cognitive, mood, sleep, sensory, and quality of life. Our objective was to produce preliminary and hypothesis-generating findings to determine whether TPS can generate clinical improvements in overall symptoms as measured by the UPDRS and further assessments. This study represents the first structured, multi-domain prospective investigation of TPS in Parkinson's disease, laying the groundwork for future randomized controlled trials.

Methods

Study design

This is an open-label, single-arm pilot study (NCT06676995) [23]. The study was conducted at the Neuromodulation Center, Spaulding Rehabilitation Hospital, Mass General Brigham and was approved by the institutional review board. All participants provided informed consent according to the Declaration of Helsinki.

Study participants

Fourteen patients aged 50–78 years with a diagnosis of "clinically established" or "clinically probable" PD were enrolled, according to the current clinical criteria [24]. Inclusion criteria required participants to be at Hoehn and Yahr stages 2–4, taking stable dopaminergic medication for at least 30 days. Key exclusion criteria included Parkinson-plus syndromes, history of deep brain stimulation, uncontrolled comorbidities, history of epilepsy, schizophrenia, bipolar illness, or alcohol/drug abuse within the past six months, metal implants contraindicated for TPS, pregnancy, contraindications to MRI according to MGB screening in the Martinos-Center (i.e., pacemaker, defibrillator or wires other than sternal wires, if devices are not compatible with MRI T3 scan), bed- or wheelchair-bound patients, and non-English speakers due to speech and voice assessment. All participants performed an MRI brain scan with a 3 T Siemens Skyra MRI scanner equipped with a 20-channel head/neck coil prior to the first stimulation session for the neuronavigation system associated with the intervention.

Intervention: transcranial pulse stimulation (TPS)

TPS was performed using the NEUROLITH® system (STORZ MEDICAL AG, Tägerwilen, Switzerland), a CE-marked non-invasive brain stimulation device designed to deliver focused shockwave pulses to specific cortical and subcortical brain regions. The treatment protocol [23] consisted of 12 TPS sessions administered over 4 weeks (3 sessions per week), based on previous studies in neurodegenerative disorders [17, 19, 25], see Table 1. A flexible window of up to 6 weeks was allowed to accommodate patient scheduling or missed sessions, provided that all 12 sessions were completed.

Each session lasted approximately 50 min and involved the administration of 10,000 individual pulses. 8000 pulses were delivered to the brain at an energy flux density of 0.25 mJ/mm^2 with a repetition rate of 4 Hz and a penetration depth up to 8 cm, sufficient to modulate cortical and subcortical structures, and 2000 pulses at an energy flux density of 0.10 mJ/mm^2 and 4 Hz were provided on the foot soles. The pulses were ultrashort (~0.3 µs duration) and applied through a hand-held transducer navigated in real-time using individual high-resolution MRI scans and an infrared-based neuronavigation system. This allowed for precise spatial targeting and even distribution of the stimulation.

The 10,000 pulses were distributed across three stimulation components:

1. Individualized symptom-targeted stimulation (4000 pulses): Pulses were directed at three to four symptom-specific regions of interest (ROIs) determined by the patient's most prominent clinical symptoms. All patients received 1000 pulses bilaterally to the primary motor cortex (M1), with the remaining 3000 pulses allocated across three of the following ROIs:
    - Dorsolateral prefrontal cortex (DLPFC)—for cognitive impairment, depression, or fatigue
    - Inferior frontal cortex (including Broca's area)—for voice and speech impairment
    - Posterior parietal cortex (PPC)—for sleep dysfunction
    - Orbitofrontal cortex—for olfactory and gustatory dysfunction
2. Standardized holocranial stimulation (4000 pulses): Pulses were uniformly applied across the entire cerebral cortex to ensure broad engagement of distributed functional networks relevant to Parkinson's disease.
3. Peripheral sensory stimulation (2000 pulses): The final 2000 pulses were applied to the plantar surface of the feet, targeting peripheral afferents to potentially enhance sensorimotor integration and gait-related outcomes [26, 27].

The transducer was manually guided in a continuous, sweeping motion, ensuring full coverage of each ROI as indicated by the neuronavigation system. The location of each pulse was recorded and visualized in real-time, allowing consistent and reproducible stimulation across sessions.

Assessments

Clinical assessments were conducted at baseline, after sessions 3, 6, 9 and 12, and at follow-up one month later. Evaluations were conducted during the patients' "ON" medication state. The primary outcome was the Unified Parkinson's Disease Rating Scale (UPDRS) Total.

Secondary outcomes included UPDRS Parts I, II, III and IV; the Non-Motor Symptoms Scale (NMSS); the SCOPA-COG for cognition; the PDQ-39 for quality of life; the Beck Depression Inventory (BDI-II); the Parkinson's Disease Sleep Scale-2 (PDSS-2); the Parkinson's Disease Fatigue Scale (PFS-16); the Freezing of Gait Questionnaire (FOGQ); voice assessments using the Voice Handicap Index (VHI-10); visual analog mood scale (VAMS); visual analog scales (VAS) for smell and taste perception, and Time Up and Go (TUG) test.

Safety, acceptability, and feasibility of intervention measures (AIM and FIM)

Side effects were assessed after each stimulation session using a standardized questionnaire. Acceptability and feasibility were measured with validated AIM and FIM questionnaires [28], and Patient's Qualitative Assessment of Treatment-Real-World (PQAT-RW) [29]. EEG recordings and brief neurological exams were performed at baseline and across key visits to monitor for neurophysiological changes or side effects.

Electroencephalography (EEG)

Resting-state EEG was recorded for 20 min (10 min eyes opened and 10 min eyes closed) at baseline, immediately after the first TPS session, after every three TPS sessions (sessions 3, 6, 9 and 12), and at the follow-up visit using a 64-channel EGI system (EGI, Eugene, OR, USA). Continuous recording allowed real-time monitoring of epileptiform activity to ensure participant safety. For the quantitative analysis, we assessed the EEG data from the baseline, after 6 sessions, after 12 sessions and follow-up. During our standard preprocessing, the final 9 min of artefact-free eyes-closed EEG were retained, and relative power was computed for each frequency band. The EEG preprocessing method followed our standard pipeline using EEGLAB in MATLAB (The MathWorks Inc., Natick, MA, USA 2024) [30] which includes (i) downsampling of 250 Hz, and filtering

Table 1 Illustration of the subject's schedule per visit

	Consent and screening	MRI visit	Baseline exam	Intervention sessions									Follow-up
	V1	V2	V3	V4 Session 1	V5 Session 2	V6 Session 3	V7 – 8 Session 4–5	V9 Session 6	V10 – 11 Session 7–8	V12 Session 9	V13 – 14 Session 10–11	V15 Session 12	V16
Medical/family history, medication and demographics	X												
Screening	X												
MRI		X											
Pregnancy test (if applicable)	X			X			X			X			
Clinical assessments			X			X		X		X		X	X
TPS—intervention				X	X	X	X	X	X	X	X	X	
Side effect questionnaire				X	X	X	X	X	X	X	X	X	
EEG			X	X		X		X		X		X	X
Acceptability questionnaire				X								X	
PQAT-RW												X	

V visit, *PQAT-RW* Patient's Qualitative Assessment of Treatment-Real-World

(1–60 Hz), (ii) visual inspection, (iii) reference to the average of all electrodes, (iv) independent component analysis (ICA), and (v) ICLables.

Power spectral density was computed using fast Fourier transform with two 2-s window, and relative power values were extracted for standard frequency bands: delta (1–3.9 Hz) theta (4–7.9 Hz), alpha (8–12.9 Hz), and beta: (13–30 Hz) in the frontal (E2, E3, E5, E6, E8, E9, E10, E11, E12, E13, E14, E19, E56, E57, E59, E60), central (E4, E7, E15, E16, E20, E21, E22, E41, E49, E50, E51, E53, E54), and parietal (E26, E27, E28, E30, E31, E33, E34, E36, E38, E40, E42, E44, E45, E46) regions as demonstrated in our previous protocol [31]. Derived indices included theta/alpha and theta/beta ratios and frontal alpha asymmetry. To determine asymmetry, the relative alpha power was natural log-transformed and was calculated by the formula: (average of right frontal) minus (relative power of left frontal), a similar method already applied in previous studies [32, 33]. The increase in alpha activity and alpha frontal asymmetry has been investigated as a potential marker of the placebo effect [34, 35]. Analyses focused on changes from baseline to post-treatment and correlations with clinical outcomes.

Statistical analysis

The primary efficacy analysis focused on the overall change in motor and non-motor symptoms, as assessed by the Unified Parkinson's Disease Rating Scale (UPDRS) Total score. These outcomes were analyzed using linear mixed-effects models to account for repeated measures across five timepoints (baseline, session 3, session 6, session 9, session 12, and follow-up). Models included fixed effects for time and random intercepts for participants to capture within-subject variability. The linearity of the change over time was tested using both linear and quadratic terms, and the best-fitting model was selected based on significance, fit indices, and visual inspection of residuals.

To evaluate clinical significance and time-specific comparisons, paired *t* tests were conducted between baseline and each post-intervention visit (session 12 and follow-up in particular). These were used to validate findings from the mixed model and to report specific within-subject changes at the primary (session 12) and follow-up endpoints. Effect sizes were calculated using Cohen's *d*, with $d > 0.5$ considered a moderate effect and $d > 0.8$ considered large. These effect sizes were also compared against published minimal clinically important difference (MCID) thresholds (≥ 5 points for UPDRS Total, ≥ 2.5 points for UPDRS Part III) to evaluate clinical relevance.

For secondary outcomes—including non-motor symptoms (NMSS), cognition (SCOPA-COG), quality of life (PDQ-39), mood (BDI-II), sleep (PDSS-2), fatigue (PFS-16), freezing of gait (FOGQ), voice (VHI-10), VAS smell and taste and TUG—paired *t* tests were similarly used to compare baseline to the primary endpoint (after session 12) and at follow-up scores. In these exploratory analyses, effect sizes were also computed and interpreted in the context of clinical thresholds.

The study was powered as a pilot to detect large within-subject effects (Cohen's $d = 1.5$) in UPDRS Total scores, with 80% power and $\alpha = 0.05$. A total of 14 participants were enrolled, consistent with power calculations and typical recommendations for early-phase pilot trials.

All analyses were performed using R (v4.2.2) and STATA (v17.0). Statistical significance was set at $p < 0.05$ (two-tailed). Given the exploratory nature of the study, no correction was applied for multiple comparisons; instead, emphasis was placed on effect size magnitude and consistency across related outcomes.

Results

Participants

Fourteen subjects with PD were included in this study. The mean age was 69.36 years (SD 8.53), ranging between 50 and 78 years old, with a predominance of males (71.43%). Most participants were married (64.28%) and retired (71.43%). The majority identified themselves as white (92.85%) and not Hispanic or Latino (92.85%). Regarding educational level, half had completed postgraduate studies (50%), while 42.85% held a 4-year college degree. Disease severity, based on the Hoehn & Yahr scale, was mostly concentrated in stages 2 (35.70%) and 2.5 (50%). The average Levodopa Equivalent Dose (LED) was 681.79 mg (SD 644), ranging between 0 and 2540 mg, and participants had a mean of 2.29 comorbidities (SD 2.0). A minority reported a history of smoking (28.57%), while 71.43% consumed alcoholic beverages, as displayed in Table 2. The mean and SD of clinical outcomes for each time point since baseline until follow-up are displayed in Table 3 and Supplementary Table 1.

UPDRS total score analysis—primary endpoint (session 12)

The mixed-effects model revealed a significant linear improvement in UPDRS Total scores over the 4-week treatment period ($\beta = -0.848$, SE = 0.292, $z = -2.906$, $p = 0.004$). The quadratic term was not significant ($\beta = 0.010$, SE = 0.019, $z = 0.513$, $p = 0.608$), indicating a predominantly linear trajectory of improvement. At the primary endpoint (session 12), patients demonstrated a mean reduction of 9.43 points in UPDRS Total scores compared to baseline (baseline: 47.79 ± 16.56; session 12: 38.36 ± 17.72), representing

Table 2 Demographics and clinical characteristics, $n = 14$

Characteristics	Mean (SD) or *n* (%)
Age	69.36 (8.53)
Sex	
Female	4 (28.57%)
Male	10 (71.43%)
Marital status	
Single	4 (28.57%)
Married	9 (64.28%)
Widowed	1 (7.1%)
Employment	
Full-time job	4 (28.57%)
Retired	10 (71.43)
Ethnicity	
Not Hispanic or Latino	13 (92.85%)
Unknown/not reported	1 (7.15%)
Race	
White	13 (92.85%)
Unknown/not reported	1 (7.15%)
Education level	
High School graduate	1 (7.15%)
4-Year college	6 (42.85%)
Postgraduate	7 (50%)
Hoehn and Yahr	
Stage 2	5 (35.70%)
Stage 2.5	7 (50%)
Stage 3	1 (7.15%)
Stage 4	1 (7.15%)
Levodopa equivalent dose (LED)	681.79 (644)
Number of comorbidities	2.29 (2.0)
History of smoking	
Yes	4 (28.57%)
No	10 (71.43)
Alcoholic beverage	
Yes	10 (71.43)
No	4 (28.57%)

a 19.7% improvement. This change was statistically significant (paired *t* test: $t = -6.27$, $p < 0.001$) with a medium effect size (Cohen's $d = -0.566$) and exceeded the minimal clinically important difference threshold of 4.5 points [36], see Fig. 1.

A strong linear dose–response relationship was observed across all treatment visits (Pearson $r = -0.946$, $p = 0.015$). Progressive improvements were evident at each timepoint: after session 3, subjects showed a 2.29-point reduction (4.8% improvement, Cohen's $d = -0.137$). By session 6 demonstrated a 10.48-point reduction (21.9% improvement, Cohen's $d = -0.617$), and after session 9 showed a 9.00-point reduction (18.8% improvement, Cohen's $d = -0.540$). At the primary endpoint, session 12, this effect reached a 9.43-point reduction (19.7% improvement, Cohen's $d = -0.566$). Follow-up assessments demonstrated sustained benefits, with a mean 10.22-point reduction relative to baseline, representing a 21.4% improvement. Effect sizes progressed from small at session 3 to medium by session 9–12, indicating clinically meaningful improvements that strengthened over time.

All improvements from session 6 onwards exceeded the established minimal clinically important difference threshold for UPDRS Total scores (≥ 5 points). The primary endpoint at session 12 demonstrated both statistical significance and clinical meaningfulness, with the magnitude of improvement representing a clinically relevant enhancement in motor function and overall disease severity. The sustained benefits and even improvements observed at the follow-up visit further support the clinical utility and durability of the therapeutic intervention.

The mixed-effects model demonstrated good predictive accuracy, with model-predicted changes closely aligning with observed improvements. At session 12, the model predicted a 10.54-point reduction compared to the observed 9.43-point reduction, indicating robust model performance and supporting the validity of the linear trajectory findings.

UPDRS Part III score analysis

The mixed-effects model revealed a significant linear improvement in UPDRS Part III scores over the 12 sessions ($\beta = -0.588$, SE = 0.184, $z = -3.193$, $p = 0.001$). The quadratic term was not significant ($\beta = 0.016$, SE = 0.012, $z = 1.353$, $p = 0.176$), indicating a predominantly linear trajectory of improvement. At the primary endpoint (session 12), patients demonstrated a mean reduction of 4.93 points in UPDRS Part III scores compared to baseline (baseline: 30.86 ± 10.56; session 12: 25.93 ± 10.39), representing a 16.0% improvement. This change was statistically significant (paired *t* test: $t = -5.274$, $p < 0.001$) with a medium effect size (Cohen's $d = -0.498$) and exceeded the minimal clinically important difference threshold of 2.5 points for motor symptoms [36], see Fig. 2.

A strong linear dose–response relationship was observed across all treatment visits (Pearson $r = -0.924$, $p = 0.025$). Progressive improvements were evident at each timepoint: session 3 showed a 1.86-point reduction (6.0% improvement, Cohen's $d = -0.188$), session 6 demonstrated a clinically relevant 6.24-point reduction (20.2% improvement, Cohen's $d = -0.575$), session 9 showed a 4.36-point reduction (14.1% improvement, Cohen's $d = -0.441$), and session 12 achieved a 4.93-point reduction (16.0% improvement, Cohen's $d = -0.498$). Effect sizes progressed from small at session 3 to medium by session 6, 9 and 12, indicating clinically meaningful improvements in motor function that strengthened over time [36, 37].

Table 3 Clinical variables across the visits at baseline, session 12 and follow-up

Variable	Baseline Mean (SD)	Session 12 Mean (SD)	Follow-up Mean (SD)	ΔSession 12 to baseline (%)	ΔFollow-up to baseline (%)
UPDRS Total	47.79 (16.56)	38.36 (17.72)	37.57 (18.49)	− 9.43 (− 19.7%)	**− 10.22# (− 21.4%)**
UPDRS III	30.86 (10.56)	25.93 (10.39)	25.86 (10.98)	− 4.93 (− 16.0%)	**− 5.00# (− 16.2%)**
UPDRS I	2.64 (1.95)	**1.79** (1.37)	**1.79** (1.58)	**− 0.85# (− 32.2%)**	**− 0.85# (− 32.2%)**
UPDRS II ON	10.93 (5.86)	8.07 (5.86)	**7.93** (6.58)	- 2.86 (- 26.2%)	**- 3.00# (- 27.4%)**
UPDRS II OFF	11.93 (7.18)	9.14 (8.35)	**8.00** (7.72)	- 2.86 (- 26.2%)	**- 3.93# (- 32.9%)**
UPDRS IV	3.36 (2.27)	2.36 (2.65)	**2.14** (2.96)	- 1.00 (- 29.8%)	**- 1.22# (- 36.3%)**
UPDRS V	2.46 (0.54)	2.46 (0.54)	2.54 (0.50)	**0.00# (0.0%)**	0.08 (3.3%)
UPDRS VI	90.00 (5.55)	92.86 (7.26)	**92.86** (6.11)	**2.86# (3.2%)**	**2.86#(3.2%)**
NMSS	47.71 (26.99)	28.57 (21.27)	**28.00** (26.72)	− 19.14 (− 40.1%)	**− 19.71# (− 41.3%)**
SCOPA COG	28.86 (5.40)	36.14 (7.04)	**36.29** (6.29)	7.28 (25.2%)	**7.43# (25.7%)**
PDQ-39 SI	3.56 (1.98)	2.26 (1.97)	**2.02** (2.04)	− 1.30 (− 36.5%)	**− 1.54# (− 43.3%)**
BDI-II	8.50 (5.83)	5.07 (4.76)	**4.93** (6.04)	− 3.43 (− 40.4%)	**− 3.57# (− 42.0%)**
PDSS-2	17.71 (11.18)	**10.79** (8.51)	11.00 (10.38)	**− 6.92# (− 39.1%)**	− 6.71 (− 37.9%)
PFS-16	4.43 (4.50)	3.00 (4.26)	**2.50** (3.92)	- 1.43 (- 32.3%)	**- 1.93# (- 43.6%)**
FOGQ	5.50 (4.64)	4.93 (5.59)	4.93 (5.24)	**- 0.57# (- 10.4%)**	**- 0.57# (- 10.4%)**
VHI-10	7.00 (5.52)	7.50 (9.31)	6.71 (7.17)	0.50 (7.1%)	**- 0.29# (- 4.0%)**
VAMS	16.57 (11.94)	9.64 (8.06)	**9.50** (6.35)	- 6.93 (- 41.8%)	**- 7.07# (- 42.7%)**
VAS SMELL	5.00 (4.06)	2.86 (3.55)	3.00 (3.49)	**- 2.14# (- 42.8%)**	- 2.00 (- 40.0%)
VAS TASTE	3.00 (3.04)	1.79 (2.83)	2.36 (3.20)	**- 1.21# (- 40.3%)**	- 0.64 (- 21.3%)
TUG	11.90 (4.14)	10.69 (0.75)	10.50 (1.09)	- 1.21 (- 10.2%)	**- 1.40# (- 11.8%)**

Values in bold indicate the greatest improvement, and those marked with # show the largest difference in effect compared to the baseline

UPDRS The Unified Parkinson's Disease Rating Scale Total score. *Part I* Mentation, Behavior, Mood. *Part II* Activities of Daily Living. *Part III* Motor Examination. *Part IV* Complications of Therapy. *Part V* Modified Hoehn and Yahr Scale. *Part VI* Schwab and England ADL Scale: patient's independence in daily activities. *NMSS* Non-Motor Symptoms Scale. *SCOPA-COG* Scales for Outcomes in Parkinson's disease-COGnition; *PDQ-39 SI* Parkinson's Disease Questionnaire-39 Summary Index. *BDI-II* Beck Depression Inventory. *PDSS-2* Parkinson's Disease Sleep Scale. *PFS-16* Parkinson's Disease Fatigue Scale. *FOGQ* Freezing of Gait Questionnaire. *VHI-10* Voice Handicap Index. *VAMS* Visual Analog Mood Scale. *VAS* Visual Analog Scale for Smell and Taste. *TUG* Time up and go

To assess the sustained treatment effects on motor symptoms, patients were evaluated one month (follow-up) after the primary endpoint. The mean UPDRS Part III score at follow-up was 25.86 ± 10.98, representing a slight improvement from session 12 (change: − 0.07 points, − 0.2%). This finding indicates successful maintenance of motor symptom improvements beyond the primary treatment period.

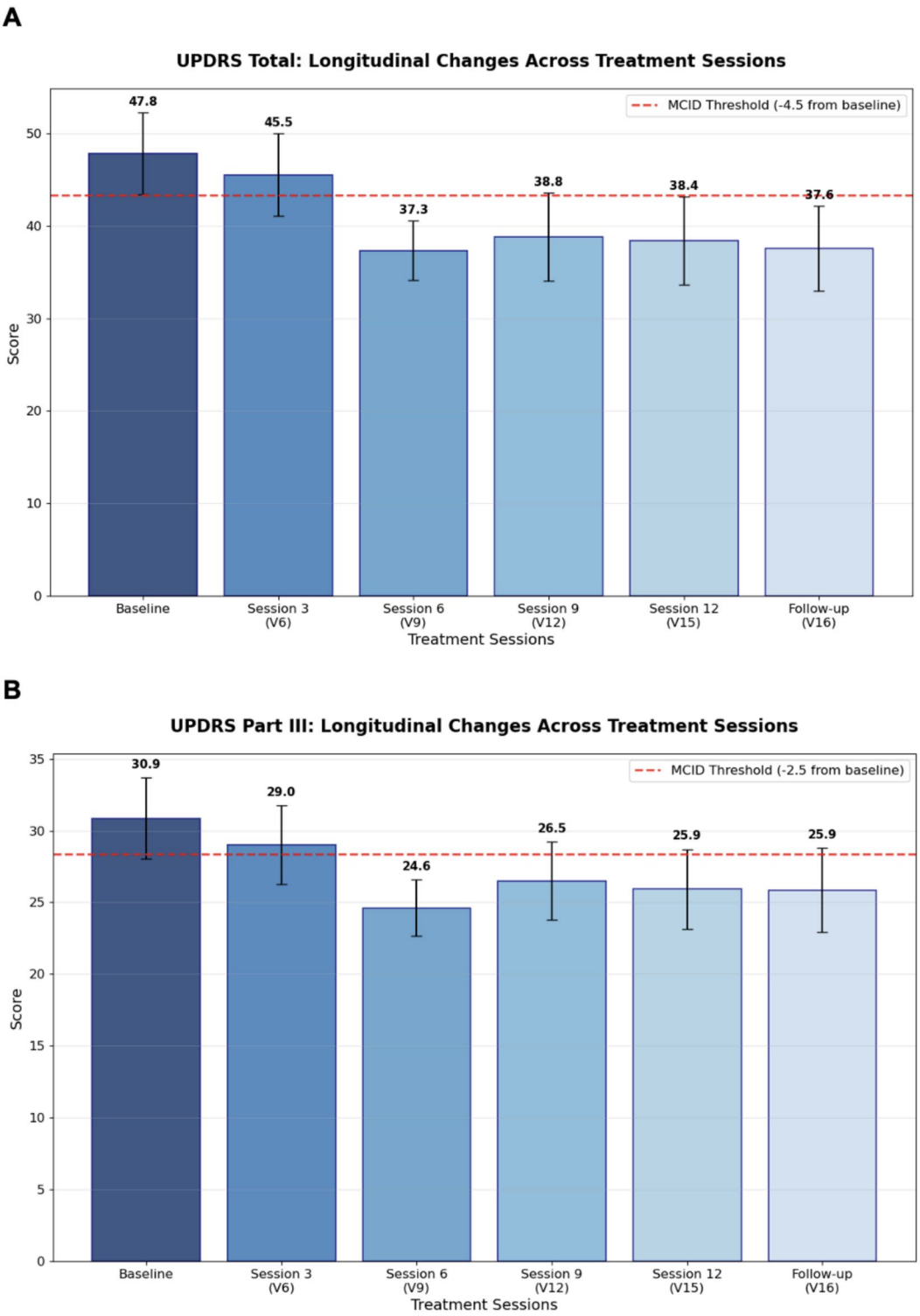
All improvements from session 6 onwards exceeded the established minimal clinically important difference threshold for UPDRS Part III scores (≥ 2.5 points). The primary endpoint at session 12 demonstrated both statistical significance and clinical meaningfulness, with the magnitude of improvement representing a clinically relevant enhancement in motor function. The sustained benefits were observed at the follow-up visit. The reduction of 5.00 points (16.2% improvement) further supports the clinical utility and durability of the therapeutic intervention for motor symptoms.

The mixed-effects model demonstrated excellent predictive accuracy for motor symptoms, with model-predicted changes closely aligning with observed improvements. At session 12, the model predicted a 5.20-point reduction compared to the observed 4.93-point reduction, indicating robust model performance and supporting the validity of the linear trajectory findings for motor function improvements.

UPDRS parts I, II, and IV

For UPDRS Part I (Non-Motor Aspects of Daily Living), baseline scores averaged 2.64 ± 1.95, which improved to 1.79 ± 1.37 at session 12, representing a mean change of − 0.85 points (95% CI: − 1.41 to − 0.31; $t(13) = -3.379$, $p = 0.005$), equivalent to a 32.4% reduction and a medium effect size (Cohen's $d = -0.487$). Significant improvements were sustained at follow-up (mean: 1.79 ± 1.58), corresponding to a − 0.85-point change from baseline (32.2% improvement).

For UPDRS Part II (Motor Aspects of Daily Living, ON state), scores decreased from 10.93 ± 5.86 at baseline to 8.07 ± 5.86 at session 12, yielding a mean reduction of − 2.86 points (95% CI: − 4.20 to − 1.52; $t(13) = -4.616$, $p < 0.001$), a 26.2% significant improvement and a moderate effect size ($d = -0.501$). At follow-up, scores further



improved to 7.93, corresponding to a − 3.00-point change from baseline (27.4% improvement).

For UPDRS Part IV (Motor Complications), participants demonstrated a reduction from 3.36 ± 2.27 at baseline to 2.36 ± 2.65 at session 12 (mean change: − 1.00; 95% CI: − 1.76 to − 0.24; $t(13) = -2.88$, $p = 0.013$), amounting to a 29.8% improvement ($d = -0.391$). At follow-up, scores further improved to 2.14, corresponding to − 1.22-point change from baseline (36.3% improvement).

From here on, due to text constraints, values are reported only as mean values and not with SD, which can be found in Table 3 and Supplementary Table 1.

◂**Fig. 1** UPDRS scores from baseline through 4-week treatment. Bars represent group means with standard error of the mean (SEM). The red dotted line indicates the minimal clinically important difference (MCID) from the baseline. **A** UPDRS Total demonstrated significant linear improvement ($\beta = -0.848$, $p = 0.004$; $r = -0.946$, $p = 0.015$). Percentage values on treatment bars show improvement from baseline, indicating statistical significance at the primary endpoint ($p < 0.001$, Cohen's $d = -0.566$). Progressive reductions exceeded the MCID threshold from Session 6 onwards, with the primary endpoint achieving a clinically meaningful 19.7% improvement. Lower UPDRS Total scores indicate better outcomes and reduced disease severity. **B** UPDRS Part III—Motor Score showed significant linear improvement ($\beta = -0.588$, $p = 0.001$; $r = -0.924$, $p = 0.025$), and statistical significance improvement at the primary endpoint ($p < 0.001$, Cohen's $d = -0.498$). Progressive reductions exceeded the MCID threshold from Session 6 onwards, with the primary endpoint achieving a clinically meaningful 16.0% improvement in motor function. Lower UPDRS Part III scores indicate better motor function and reduced motor symptom severity

Non-motor Symptoms Scale (NMSS)

Among the 14 participants with complete data, non-motor symptom burden—as measured by the NMSS—decreased significantly over the course of TPS treatment. Scores declined from a baseline mean of 47.71 to 28.57 by session 12, reflecting a 19.14-point (40.1%) reduction, exceeding the MCID of − 13.91 points [38] ($p = 0.014$, Cohen's $d = -0.754$), see Fig. 2. The greatest improvement occurred between sessions 3 and 6 ($p = 0.001$, $d = -0.416$), followed by a plateau and slight rebound by session 9, with sustained benefit through session 12. The biggest change to baseline was achieved at follow-up with 28.00 points, reflecting a 19.71-point (41.3%) reduction. Linear modeling showed a strong overall trend ($R^2 = 0.84$, $p = 0.029$), though the response was best characterized as biphasic-featuring a rapid early reduction followed by stabilization.

Cognitive performance (SCOPA-COG)

Cognitive performance, as measured by the SCOPA-COG, improved consistently over the four-week TPS treatment period. Mean baseline scores were 28.86, increasing to 34.31 at session 3, 35.85 at session 6, 34.43 at session 9, and 36.14 at session 12. This progression reflects a total increase of 7.28 points, corresponding to a 25.2% improvement from baseline. The biggest change to baseline was achieved at follow-up with 36.29 points, reflecting a 7.43-point (25.7%) increase.

All weekly comparisons to baseline indicated statistically and clinically significant improvements. From baseline to session 3, participants showed a gain of 5.45 points, representing an 18.9% improvement with a large effect size (Cohen's $d = 1.174$). At session 6, the improvement reached 6.99 points (24.2% increase, $d = 1.650$). By session 9, the mean change was 5.57 points (19.3% increase, $d = 0.858$). The session 12 score reflected the highest absolute gain of 7.28 points, a 25.2% improvement from baseline, with a corresponding effect size of $d = 1.161$.

While the overall trajectory was upward, the pattern of improvement was non-linear. The most substantial gain occurred from baseline to session 3, followed by a smaller increase to session 6. A slight decline was observed at session 9, after which scores rose again at session 12, with continued improvement evident in the one-month follow-up score.

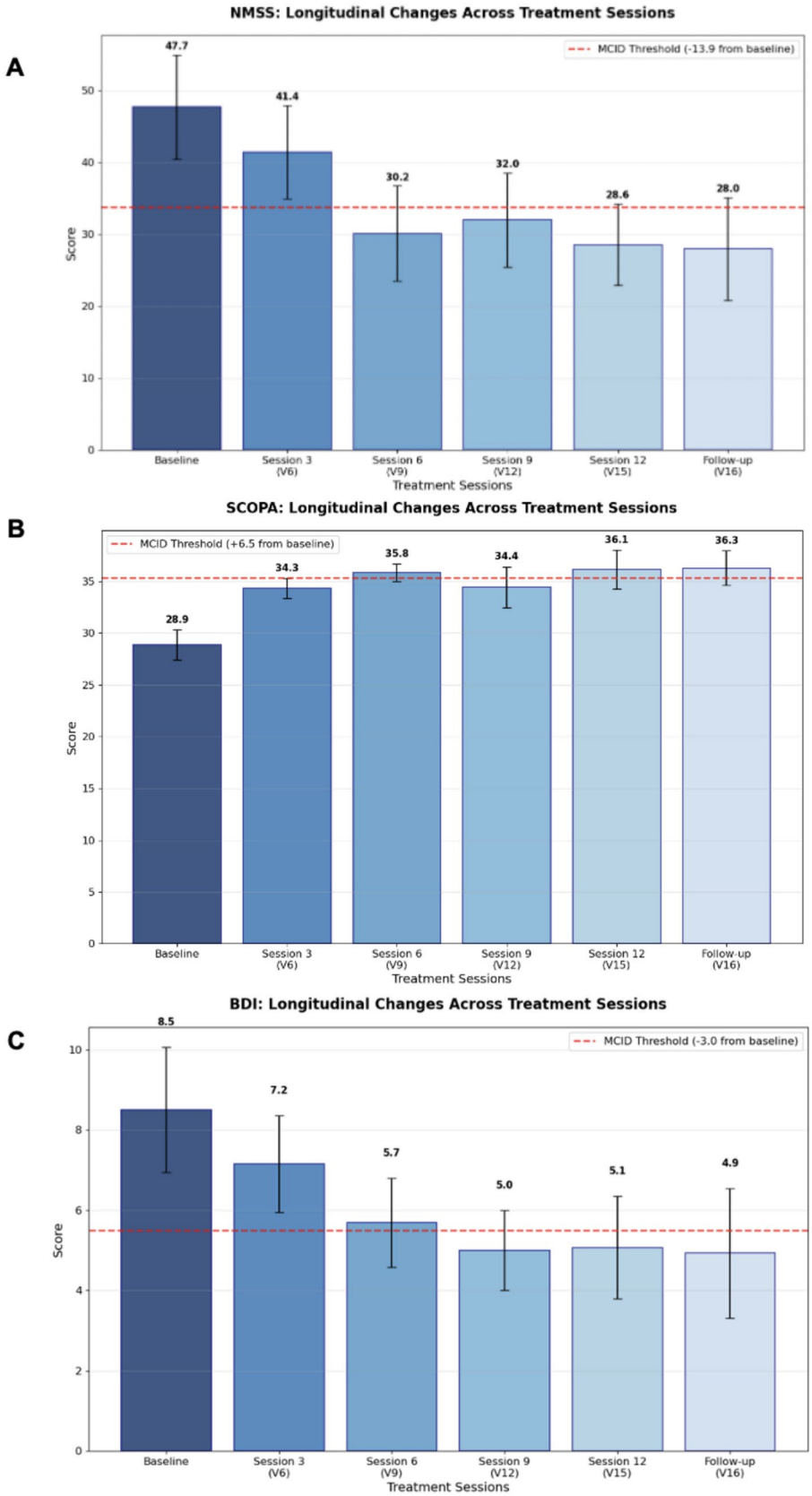
The increase of 7.28 points from 28.86 at baseline to 36.14 at session 12 represents a robust and clinically meaningful enhancement of cognitive abilities (above 6.5 points) [39] over a short intervention period.

Beck Depression Inventory (BDI-II)

Participants experienced a progressive reduction in depressive symptoms over the 12 TPS sessions, with BDI-II scores decreasing from 8.50 at baseline to 5.07 at session 12, a 3.43-point (40.4%) improvement, and to 4.93 at follow-up, a 3.57-point (%) improvement, both exceeding the minimal clinically important difference (MCID) of 3 points. Statistically significant reductions emerged by session 6 ($p = 0.037$, $d = -0.570$) and continued improving at session 9 ($p = 0.004$, $d = -0.715$), with sustained benefit through session 12 ($p = 0.008$, $d = -0.644$), and peaked at follow-up ($p = 0.002$, $d = -0.602$), see Fig. 2. While the overall trend was downward, the trajectory followed a non-linear course, with early rapid gains followed by stabilization and a slight rebound. Linear modeling showed a strong correlation ($R^2 = 0.886$, $p = 0.017$), but a quadratic model ($R^2 = 0.987$) provided a superior fit, supporting a biphasic pattern of improvement.

Sleep quality (PDSS-2) and quality of life outcomes (PDQ-39 SI)

Participants experienced significant improvements in both sleep quality and overall quality of life throughout the intervention period. Sleep disturbances, measured by the Parkinson's Disease Sleep Scale-2 (PDSS-2), demonstrated a consistent linear decline across sessions, with scores decreasing from a baseline mean of 17.71 to 10.79 at session 12, a 39.1% reduction surpassing the minimal clinically important difference (MCID) of − 3.44 points [40]. A linear mixed-effects model confirmed a significant trend of improvement (slope = − 0.80 per three sessions, 95% CI: − 1.18 to − 0.41, $p < 0.001$), corresponding to a predicted 6.38-point reduction by follow-up. Effect sizes increased over time, culminating in a large and significant improvement at session 12 ($p = 0.011$, Cohen's $d = -0.698$).


A
NMSS: Longitudinal Changes Across Treatment Sessions
MCID Threshold (-13.9 from baseline)
47.7
41.4
30.2
32.0
28.6
28.0
Score
Baseline
Session 3 (V6)
Session 6 (V9)
Session 9 (V12)
Session 12 (V15)
Follow-up (V16)
Treatment Sessions
B
SCOPA: Longitudinal Changes Across Treatment Sessions
MCID Threshold (+6.5 from baseline)
28.9
34.3
35.8
34.4
36.1
36.3
Score
Baseline
Session 3 (V6)
Session 6 (V9)
Session 9 (V12)
Session 12 (V15)
Follow-up (V16)
Treatment Sessions
C
BDI: Longitudinal Changes Across Treatment Sessions
MCID Threshold (-3.0 from baseline)
8.5
7.2
5.7
5.0
5.1
4.9
Score
Baseline
Session 3 (V6)
Session 6 (V9)
Session 9 (V12)
Session 12 (V15)
Follow-up (V16)
Treatment Sessions

◂**Fig. 2** Non-motor symptoms from baseline through 4-week treatment. Bars represent group means with standard error of the mean (SEM). Total score values on treatment bars show improvement from baseline. The red dotted line indicates the minimal clinically important difference (MCID) from the baseline. **A** NMMS demonstrated significant linear improvement (R^2= 0.838, p = 0.029). Percentage values on treatment bars show improvement from baseline, indicating statistical significance at the primary (p = 0.014, Cohen's d = − 0.754). Progressive reductions exceeded the MCID threshold from Session 6 onwards, with the primary endpoint achieving a clinically meaningful improvement below 13.91 points the MCID. Lower NMSS score indicate better outcomes and reduced disease severity. **B** The graph shows SCOPA-COG cognitive assessment scores across 5 timepoints, with bars representing group means ± SEM and the connecting line showing the overall trajectory of cognitive changes during treatment. Weekly comparisons to baseline showed significant and clinically meaningful improvements. At session 3, participants improved by 5.45 points (18.9%, d = 1.174); at session 6, by 6.99 points (24.2%, d = 1.650); at session 9, by 5.57 points (19.3%, d = 0.858); and at session 12, by 7.28 points (25.2%, d = 1.161). The greatest absolute gain was achieved at follow-up with 7.43 points improvement (25.7%, d = 1.268). **C** BDI-II Score shows a biphasic treatment trajectory with peak improvement at Session 9, followed by slight plateau (R^2 = 0.886, p = 0.017 linear; R^2 = 0.987 quadratic model). MCID threshold was achieved from session 6 onwards, with continued improvement of − 41.2% at session 9 (Cohen's d = 0.947, large effect) and sustained benefit of − 40.4% at the primary endpoint session 12 (Cohen's d = − 0.644, large effect) and a peak improvement of − 42.0% at follow-up. All scores remained in the minimal depression range throughout treatment. Lower BDI-II scores indicate reduced depressive symptom severity

Similarly, the Parkinson's Disease Questionnaire-39 Summary Index (PDQ-39 SI) revealed a significant and sustained enhancement in quality of life. Scores declined from a baseline mean of 3.56 points to 2.26 at session 12, improving to 2.02 points at follow-up, which corresponds to 36.5% and 43.3% improvements, respectively. The mixed effects model estimated a reduction of − 1.35 points at session 12 (d = − 0.69; p = 0.005) and − 1.54 points at follow-up (p = 0.002). Effect sizes were large and statistically significant from session 6 onward, peaking at follow-up (p = 0.001, d = − 0.769). These findings collectively demonstrate robust clinical gains in both sleep and quality of life metrics throughout the intervention.

Change score correlation analysis

Correlation analysis of change scores from baseline to the primary endpoint (session 12) revealed distinct patterns of treatment response across symptom domains (Fig. 3). While motor symptom improvements showed strong internal consistency (UPDRS II ON/OFF changes: r = 0.89), cross-domain correlations were generally moderate to low, suggesting partially independent therapeutic mechanisms. Notably, motor (UPDRS III) and non-motor (NMSS) symptom improvements showed minimal correlation ($r \approx 0.1$), indicating that TPS benefits extend beyond simple motor enhancement. Sleep improvements (PDSS-2) demonstrated moderate correlations with multiple domains (r = 0.3–0.5), suggesting sleep enhancement as a potential central therapeutic mechanism. These findings support TPS as a multimodal therapeutic intervention with broad benefits across the spectrum of Parkinson's disease symptoms.

Treatment effects and follow-up outcomes

At follow-up, all clinical outcomes demonstrated statistically significant improvements from baseline, highlighting the robust impact of the intervention across multiple domains of Parkinson's disease. Specifically, there was a 21.4% reduction in the UPDRS Total score (p < 0.001, Cohen's d = − 0.582), and a 16.2% reduction in the UPDRS Part III motor score (p < 0.001, d = − 0.464), both reflecting large effect sizes. Non-motor symptoms, assessed by the NMSS, showed a 41.3% reduction (p = 0.02, d = − 0.71), while depressive symptoms, as measured by the BDI-II, decreased by 42.0% (p = 0.002, d = − 0.602). Sleep quality, PDSS-2, improved by 37.9% (p = 0.01, d = − 0.622), and quality of life, measured by the PDQ-39 SI, showed a 43.3% reduction in burden (p = 0.001, d = − 0.769).

To evaluate the sustained treatment effects, scores at the follow-up visit were compared with those at the main endpoint (session 12). No statistically significant differences were observed between these timepoints across any of the measures (all p values > 0.05), with small effect sizes (d < 0.5) and minimal percentage changes (< 18%). This suggests that the clinical benefits achieved by session 12 were well maintained through the follow-up period. These findings demonstrate not only a strong initial treatment efficacy but also sustained improvements across motor, non-motor, mood, sleep, and quality of life domains, underscoring the comprehensive and durable impact of the intervention in individuals with Parkinson's disease with even better outcomes at follow-up in comparison to session 12.

For the remaining secondary outcomes, the complete set of scores is presented in the Supplementary Table 1, including the PFS-16, FOGQ, VHI-10, VAMS, VAS-smell, VAS-taste, and TUG.

EEG theta power changes

Analysis of theta power from baseline to session 12 revealed significant increases exclusively in relative theta power, whereas absolute theta power showed no significant changes across regions. Six cortical regions demonstrated significant relative theta increases: frontal (mean change = + 0.05, p = 0.005, Cohen's d = 0.354), right frontal (+ 0.06, p = 0.002, d = 0.433), central (+ 0.06, p = 0.004, d = 0.409), right central (+ 0.05, p = 0.006, d = 0.375), parietal (+ 0.05, p = 0.021, d = 0.383), and right parietal (+ 0.06, p = 0.001,

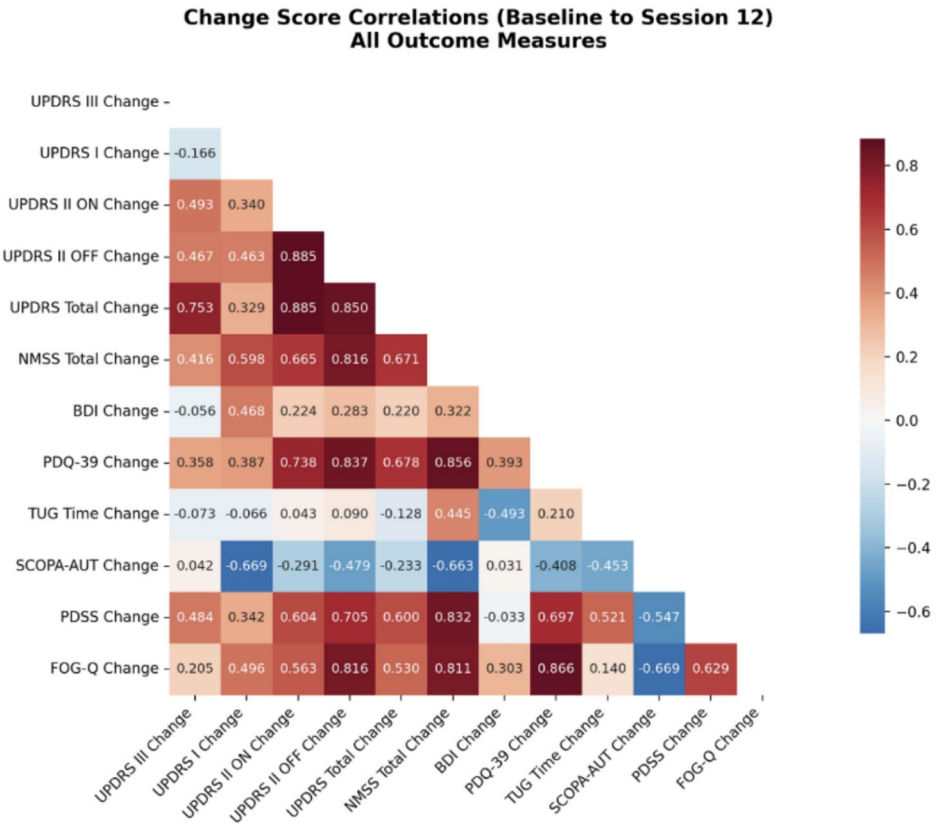


Fig. 3 Change score correlation matrix for TPS treatment response. Correlation heatmap showing relationships between symptom domain improvements from baseline to primary endpoint (session 12). Complete correlation matrix for change scores calculated as (session 12—baseline), where negative values represent improvement for most measures except SCOPA-AUT. Correlation strength: $|r| > 0.7$ (strong), 0.3–0.7 (moderate), < 0.3 (weak). Only upper triangle displayed to avoid redundancy. Sample size: $n = 14$ patients ($n = 12$ for TUG time due to missing data). Statistical significance testing not performed due to exploratory nature and small sample size. Key findings: (1) strong correlations within motor domain components, (2) low motor-non-motor correlations suggesting independent mechanisms, (3) sleep improvements (PDSS-2) correlate moderately across multiple domains, (4) largest effect sizes in non-motor domains (BDI-II: 40.4%, NMSS: 40.1%, PDSS-2: 39.1%, PDQ-39: 36.5% improvement)

$d = 0.435$). The largest effect was observed in the right frontal region. Topographic power distribution across different time points is displayed in Fig. 4.

Theta/beta index changes (baseline vs session 12)

Analysis of the theta/beta index from baseline to session 12 revealed significant increases across all examined cortical regions, indicating a consistent modulation of oscillatory activity. In the frontal region, the theta/beta index increased significantly ($p = 0.039$; Wilcoxon $p = 0.009$), with the mean value rising from 4.37 at baseline to 6.16 at session 12 (mean change = + 1.79; Cohen's $d = 0.308$). The central region also demonstrated a significant increase ($p = 0.036$; Wilcoxon $p = 0.013$), with a mean change of + 1.993 (from 4.78 to 6.77), corresponding to a small effect size ($d = 0.238$). Similarly, the parietal region showed a significant increase ($p = 0.014$; Wilcoxon $p = 0.003$), with the mean theta/beta index increasing from 4.95 to 6.89 (mean change = + 1.935) and a small effect size ($d = 0.284$).

Theta/alpha index changes (baseline vs session 12)

Comparisons of the theta/alpha index between baseline and session 12 demonstrated significant and consistent increases across all examined cortical regions. In the frontal region, the theta/alpha index increased significantly ($p = 0.029$; Wilcoxon $p = 0.003$), with a mean change of + 0.42 (rising from 0.94 at baseline to 1.36 at session 12; Cohen's $d = 0.335$), indicating a potential modulation of oscillatory activity. The central region also showed a significant increase ($p = 0.008$; Wilcoxon $p = 0.002$), with the mean index increasing from 1.08 to 1.41(mean change = + 0.33). The effect size was small ($d = 0.199$). Similarly, the parietal region exhibited a significant increase ($p = 0.018$; Wilcoxon $p = 0.002$), with the mean value rising from 0.85 to 1.22 (mean change = + 0.37) and a small effect size ($d = 0.299$).

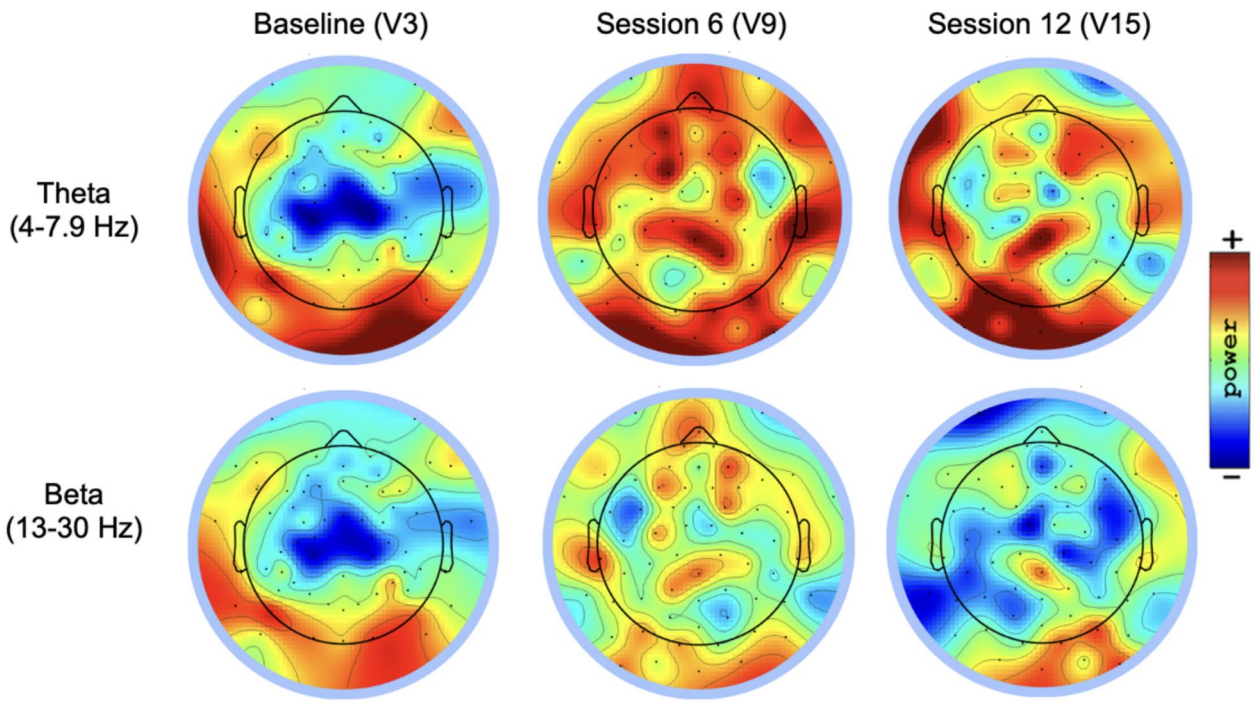


Fig. 4 Topographic distribution of scalp plots of EEG oscillations in resting-state across three time points. Theta power (4–7.9 Hz, range: 35.0–42.0 dB) (10 × log10 P) and beta power (13–30 Hz, range: 4.0–12.0 dB) (10 × log10 P). Colors (blue) represent lower power and warmer colors (red) represent higher power. An increase in theta power was observed in different cortical regions, while beta oscillations followed a tendency of reduction, after 12 sessions

Baseline theta/beta ratios as predictors of clinical response

Correlation analyses examining whether baseline theta/beta ratios predicted clinical outcomes from baseline to session 12 revealed significant associations, particularly for non-motor symptoms. Lower baseline theta/beta ratios were associated with greater improvements in NMSS score, with significant correlations observed in the parietal ($\rho = 0.678$, $p = 0.008$), central ($\rho = 0.608$, $p = 0.021$), and frontal regions ($\rho = 0.590$, $p = 0.026$). Trends were also observed for quality of life and motor symptoms, where lower parietal theta/beta ratios tended to predict better outcomes on the PDQ-39 ($\rho = 0.520$, $p = 0.057$) and greater motor improvements on the UPDRS-III ($\rho = 0.499$, $p = 0.069$). A similar trend was noted for the frontal theta/beta ratio and PDQ-39 scores ($\rho = 0.478$, $p = 0.084$). These findings suggest that a lower baseline theta/beta ratio may serve as a marker of greater responsiveness to treatment, particularly in non-motor domains, but also with indications in motor and quality-of-life outcomes.

Follow-up EEG analysis

To evaluate the stability of EEG changes beyond the treatment phase, we analyzed cortical averages of relative theta power across frontal, central, and parietal regions at follow-up visits (session 12 and follow-up). Paired comparisons of follow-up vs. session 12 values showed no significant difference in the cortical mean ($p = 0.259$), with small and negative average differences, indicating that the relative theta increase observed during treatment was not further modulated in the follow-up period. We further examined whether changes in theta–beta index (TBI) differed from those in theta–alpha index (TAI) between session 12 and follow-up. Non-parametric (Wilcoxon signed-rank) tests consistently showed no significant differences in the magnitude of change between TBI and TAI across all cortical regions. At the regional level, both indices demonstrated slight decreases from session 12 and follow-up. In the frontal cortex, decreases were comparable for TBI and TAI (Wilcoxon $p = 0.502$). The central region showed larger reductions in both indices, but the relative changes remained statistically not significant (Wilcoxon $p = 0.855$). Similarly, in the parietal region, the decline did not differ between timepoints (Wilcoxon $p = 0.715$). Taken together, these results indicate that while modest decreases in relative theta were observed at follow-up, these were consistent across indices and regions, and no significant divergence emerged between timepoints, suggesting a stable electrophysiological signature after the treatment period.

EEG rhythms associated with placebo

Alpha asymmetry increases have been reported as a placebo signature in the literature [35] and thus were analyzed here. No statistically significant changes were observed in any cortical region (all p values > 0.05); however, the general trend indicated a decrease in asymmetry (less negative values), suggesting a move toward greater interhemispheric balance. In the frontal region, asymmetry decreased (baseline: 0.005; session 12: − 0.008; mean change = − 0.013), although this change was not significant ($t = -1.13$, $p = 0.277$). The central region showed no significant change (baseline: − 0.006; session 12: 0.013; mean change = 0.02, $t = 2.07$, $p = 0.058$). The parietal region exhibited the largest numerical decrease in asymmetry (baseline: 0.030; session 12: − 0.008; mean change = − 0.022), but this difference also did not reach statistical significance ($t = -1.30$, $p = 0.216$). Overall, alpha asymmetry decreased across the frontal and parietal regions, reflecting a trend toward improved interhemispheric balance, but the group-level changes were small and not statistically significant.

Similarly, alpha oscillations have also been correlated with placebo response [34]. No statistically significant changes in alpha power were observed in any region; however, a consistent trend toward reduced alpha power was noted across all cortical regions. The largest decreases were observed in the parietal regions, particularly the right parietal cortex (mean change = − 0.023, $t = -0.85$ $p = 0.41$, $d = -0.151$) and total parietal region (mean change = − 0.04, $t = -1.26$, $p = 0.229$, $d = -0.240$), both showing small effect sizes. The central regions also demonstrated reductions, with the left central cortex (mean change = − 0.03, $t = -1.61$, $p = 0.132$, $d = -0.240$) and total central region (mean change = − 0.02, $t = -0.85$, $p = 0.410$, $d = -0.152$) showing similar small effects. While these group-level changes did not reach statistical significance ($p > 0.05$ for all comparisons), the consistent posterior and central alpha power reductions, combined with small effect sizes, suggest a potentially meaningful physiological trend.

Safety, acceptability (AIM), and feasibility (FIM)

During all 168 TPS sessions, side effects related to the stimulation were reported in only three moments: two subjects reported one event of mild pain/pressure each, and one subject reported one episode of mild headache during the intervention session. Only expected transient side effects were noted during the stimulation session, disappearing before the subjects left the hospital facilities. Additionally, after the last stimulation session, subjects were asked to complete the questionnaire about AIM and FIM, where they could select the options: "completely disagree", "disagree", "neither agree nor disagree", "agree", and "completely agree" for each statement related to the intervention. 95.5% of the answers were "agree" or "completely agree" about the acceptability and feasibility of TPS, with no "completely disagree" or "disagree" answers (see Supplementary Table 2), confirming that all patients who received TPS demonstrated satisfaction with the treatment. Results regarding the qualitative assessment (PQAT-RW) are described in the Supplementary Material.

Discussion

This prospective, open-label pilot study provides preliminary evidence that TPS is a feasible, well-tolerated, and potentially effective adjunctive intervention for individuals with Parkinson's disease. Across a 4-week protocol involving 12 TPS sessions, participants demonstrated significant and clinically meaningful overall improvements in both motor and non-motor domains. The primary outcome, UPDRS Total score, improved by an average of 9.43 points at the end of treatment (session 12) and 10.22 points at follow-up, reflecting a 21.4% overall improvement at follow-up and exceeding the MCID threshold of 5 points. UPDRS Part III motor scores followed a similar trajectory, with a 4.93-point reduction by session 12 and a 5.00-point reduction by the follow-up visit, surpassing the MCID of 2.5 points and representing a 16.2% improvement in motor function. Importantly, these improvements at session 12, along with the EEG changes observed, were maintained at follow-up, underscoring the durability of TPS effects beyond the active treatment phase.

Beyond motor symptoms, we observed significant reductions in non-motor symptom burden (NMSS), depressive symptoms (BDI-II), sleep disturbances (PDSS-2), alongside robust improvements in cognitive performance (SCOPA-COG) and quality of life (PDQ-39). These changes were consistent across multiple timepoints and frequently showed medium to large effect sizes. Improvements generally followed a linear trajectory during the active treatment phase and were sustained or even enhanced at one-month follow-up, suggesting that TPS may induce neuroplastic effects with continued benefit beyond the stimulation period. Importantly, TPS was safe and well tolerated, with no serious side effects, high treatment adherence, and favorable patient-reported acceptability.

In addition, these clinical benefits were accompanied by neurophysiological changes captured through EEG, providing objective evidence of cortical modulation and supporting the biological plausibility of TPS effects. Significant increases in theta/alpha and theta/beta ratios across frontal, central, and parietal regions suggest a shift toward theta-dominant oscillatory states, consistent with enhanced neuroplasticity, attentional regulation, and memory consolidation.

In terms of motor outcomes, in the multiple-treatments meta-analysis of 16 RCTs with 2186 patients [41], UPDRS motor outcomes were assessed in both the ON- and OFF-medication states to evaluate the effects of DBS compared to medical therapy. In the ON-medication condition, GPi-DBS improved UPDRS Part III scores by − 4.09 points, and STN-DBS by − 3.23 points, both statistically significant effects. However, improvements in UPDRS Part II (activities of daily living) during the ON state were more limited, with GPi-DBS showing a non-significant − 3.09-point change and subthalamic nucleus deep brain stimulation (STN-DBS) showing a modest but significant − 1.50-point improvement. In comparison, our TPS intervention—also assessed in the ON-medication state—yielded larger improvements, with a mean reduction of − 4.93 points in UPDRS Part III (Cohen's $d = -0.686$) and − 2.86 points in UPDRS Part II at session 12. While these TPS outcomes appear to exceed those reported for DBS in the ON state, it is important to note that our results stem from an open-label study, whereas the DBS findings were derived from randomized controlled trials. Nonetheless, the magnitude of TPS improvements highlights its promise as a non-invasive alternative with clinically meaningful benefits.

In our study, we observed a substantial reduction in non-motor symptoms among patients with Parkinson's disease, as reflected by a mean NMSS score difference of − 19.14 points from baseline (Cohen's $d = -0.754$), indicating a large effect size. This outcome compares favorably with the results reported in a recent meta-analysis of DBS studies. This meta-analysis evaluated the impact of STN-DBS on non-motor symptoms in Parkinson's disease, including 10 studies (most non-randomized trials) and a total of 338 patients [42]. The primary outcome measure was the change in NMSS score from baseline to post-intervention follow-up periods. STN-DBS produced a weighted mean difference (WMD) of − 17.73 points in NMSS score across timepoints up to 12 months. Taken together with our findings, this suggests that TPS, being non-invasive, may yield comparable or slightly greater improvements in non-motor symptoms relative to DBS. Importantly, both interventions were evaluated in open-label conditions, which should be taken into account when interpreting effect sizes.

TPS led to significant improvements in cognitive function, as reflected by a mean increase of 7.28 points in SCOPA-COG scores (Cohen's $d = 1.161$) after 12 TPS sessions, suggesting large effects on global cognition in patients with Parkinson's disease. The observed cognitive benefits with TPS are promising and suggest that further investigation in controlled trials is warranted to clarify its efficacy and comparative advantages in cognitive rehabilitation for Parkinson's disease.

This open-label pilot trial has results that would be compared to a previous retrospective study with TPS in PD. While we showed a 5.00-point reduction in UPDRS Part III at follow-up, along with cognitive and non-motor symptom gains, the earlier retrospective TPS study by Osou et al. [20] also reported a significant mean reduction in UPDRS-III from 16.70 to 12.95 points ($p < 0.001$, Cohen's $d = 1.38$) in a cohort of 20 patients undergoing ten sessions of TPS focused on the motor networks. Both studies highlight the feasibility, tolerability, and short-term effectiveness of TPS in real-world clinical settings. However, our study extended these findings by incorporating a more comprehensive evaluation, including non-motor outcomes (NMSS, SCOPA-COG, PDQ-39, BDI-II, PDSS-2, PFS-16, FOGQ, VHI-10, VAMS,VAS for smell and taste perception, and TUG) and also utilized enhanced stimulation parameters, implementing the first personalized treatment protocol tailored to the most relevant symptoms of each individual, and integrated neurophysiological evaluations through EEG.

Pre-clinical studies suggest that TPS influences "*mechanotransduction pathways*", leading to ion channel activation and downstream intracellular signaling, increased expression of vascular endothelial growth factor (VEGF) in neuronal cells, enhanced angiogenesis, and potential modulation of synaptic release of neurotransmitters such as dopamine, serotonin, and gamma-aminobutyric acid (GABA), indicating a complementary effect to the usual care in PD patient [43–45]. Our moderator analysis revealed that patients with higher baseline symptom severity showed greater clinical improvements (see Supplementary Material), a finding consistent with placebo-related patterns reported in prior literature. However, importantly, we found that higher dopaminergic medication load (LED) was associated with reduced treatment response, which contrasts with the findings from the meta-analysis by Haji et al. [46], where greater prior dopaminergic exposure was linked to stronger placebo effects. Additionally, in our cohort, age and disease duration did not significantly moderate treatment outcomes, whereas in Haji et al.'s analysis of 38 randomized controlled trials, both older age and longer disease duration were associated with weaker placebo effects [46]. The fact that our moderator pattern partially contradicts established placebo predictors, especially regarding medication load, suggests that the observed benefits of TPS are less likely to be driven purely by placebo mechanisms, despite the open-label design. This divergence supports the plausibility of a true therapeutic effect of TPS, independent of known placebo-enhancing factors.

Importantly, the findings from our open-label TPS study, showing significant improvements in objective motor outcomes and non-motor outcomes, contrast with evidence from placebo-controlled trials suggesting no objective motor benefits from placebo alone. For instance, the double-blind, crossover RCT by Fregni et al. [47] demonstrated that both placebo pills and sham TMS failed to produce

any significant objective improvement in motor function, as measured by UPDRS and multiple motor performance tests, despite participants reporting subjective improvements on a visual analog scale (VAS). Levodopa, in contrast, led to clear improvements across all objective measures. This dissociation between subjective perception and motor performance reinforces the interpretation that the motor improvements observed in our TPS study are unlikely to be solely driven by placebo effects, particularly given that the magnitude and consistency of objective change in our data exceeded what is typically seen in sham-controlled studies. These comparisons further highlight the therapeutic potential of TPS and underscore the need for future blinded trials to validate its efficacy.

The significant and consistent increases in both theta/alpha and theta/beta ratios across all cortical regions suggest a robust shift toward theta-dominant oscillatory states, indicative of enhanced neuroplasticity, memory consolidation, and attentional control. Theta enhancement relative to alpha and beta reflects a transition from hyperaroused or idle states to a more relaxed yet cognitively engaged brain state, aligning with improved learning and emotional regulation mechanisms. As relative power is expressed as a percentage of total spectral power, it is often more sensitive to detecting oscillatory changes than absolute power (μV^2), and shifts towards high- or low-frequency bands. Also, artifacts tend to increase power across all frequency bands, an effect that can be partially mitigated when power is examined in relative rather than absolute values [48].

Theta oscillation has important roles in human brain activity associated with cognitive functions, memory and emotional processing in different cortical regions [49]. Previous studies suggest a link between increased theta activity and stronger neuroplasticity for memory consolidation [50, 51]. Furthermore, clinical research indicates that theta activity may be associated with compensatory neural mechanisms in depression symptoms, memory impairments, and somatosensory outcomes [52, 53]. Ye et al. [54] also reported an abnormally reduced theta activity in the parietal region of Parkinson's disease patients, which was associated with poorer memory performance compared to healthy controls. Similar compensatory mechanisms may be reflected in an increased theta/alpha ratio, which has previously been linked to motor function recovery in stroke patients [55]. Moreover, Chan and Choi [56] reported that individuals with depression exhibit a reduced theta/beta ratio. These findings support the evidence linking altered oscillatory dynamics to mood and cognitive disorders that are present in the PD population.

Regional specificity provides further insight into functional implications. The frontal cortex, showing the strongest modulation, is associated with improved executive function, sustained attention, and emotional regulation, relevant to depression, and non-motor symptoms in PD. The parietal region changes suggest enhanced visuospatial attention and sensory integration, while the central region modulation likely reflects improved sensorimotor integration and motor learning, important for neurorehabilitation. The parallel increases across both ratios highlight theta enhancement as the primary driver of these changes, with effect sizes ($d \approx 0.35$–0.44) indicating potential meaningful responses.

Our results showing that lower baseline theta/beta ratios predicted better clinical outcomes closely parallel findings reported in stroke rehabilitation research, where higher baseline theta/alpha ratios (TAR) in the lesioned hemisphere were associated with poorer motor recovery (which, conversely indicates that lower baseline is associated with better motor gains) (DEFINE cohort, $n = 102$) [57]. In that study, lower TAR values were consistently linked to better performance on multiple motor function tests, including the Fugl-Meyer Assessment and Nine-Hole Peg Test, whereas improvements in TAR post-intervention correlated with functional motor gains. Similarly, in our cohort, patients with lower baseline theta/beta ratios exhibited greater improvements in non-motor symptoms and showed trends toward better motor and quality-of-life outcomes. These converging results suggest that baseline cortical oscillatory patterns, particularly lower theta/alpha ratios, may indicate a state where existing compensatory dynamics are suboptimal, leaving greater room for adaptive reorganization and functional improvement. In other words, patients with lower baseline theta/alpha activity may not be relying on maladaptive compensatory mechanisms, making them more responsive to neuromodulatory interventions that can enhance neuroplasticity. Together, these findings reinforce the potential of EEG-derived frequency ratios as prognostic biomarkers, not only for predicting motor recovery post-stroke but also for guiding neuromodulation-based interventions targeting both motor and non-motor symptoms.

Despite the open-label design, the observed improvements are unlikely to be attributable only to placebo effects or regression to the mean, as they demonstrate consistent and clinically meaningful improvements across multiple objective and independent domains, including motor symptoms (UPDRS-III), non-motor symptoms (NMSS), cognition (SCOPA-COG), quality of life (PDQ-39), and measures of sleep, fatigue, and mood (PDSS-2, PFS-16, BDI-II). Placebo effects typically influence subjective reports, not such a broad range of validated clinician-rated and performance-based outcomes. The observed moderate-to-large effect sizes (Cohen's $d = -0.57$ to -1.16) exceed what is commonly seen in sham-controlled trials of non-invasive brain stimulation. Notably, participants in this trial had moderate-stage Parkinson's disease, and the most advanced patient showed the least improvement, further arguing against regression to the mean as a primary driver. Taken together, these patterns

suggest that TPS may elicit true neurophysiological benefits beyond expectancy effects. Additionally, EEG can also be used as a potential marker for placebo effects. Our observations show decreases—rather than increases—in both alpha power and frontal alpha asymmetry from baseline to session 12. This diverges from established EEG signatures commonly reported in placebo responses, which typically feature increased alpha power or alpha asymmetry, especially in the frontal cortex. Although not conclusive, our EEG findings, together with the clinical follow-up results, suggest that placebo effects alone may not fully account for the observed improvements.

A previous systematic review [34] indicated that placebo responses are typically associated with increased alpha oscillations in the frontal and central regions. For instance, a study on ergogenic placebos in athletes found that receiving a fake performance aid led to a significant increase in frontal alpha asymmetry—an established correlate of positive affect and placebo-induced expectations [35]. Likewise, placebo interventions in emotion and pain studies often elicit increases in posterior alpha or frontal asymmetry [58]. In fact, our data indicate a reduction in alpha rhythms and asymmetry—particularly in frontal and parietal regions—with no statistically significant changes overall. This suggests that our neuromodulatory treatment did not induce the typical placebo-related EEG signature (i.e., elevated alpha activity), but rather the opposite: reduced cortical alpha activity, which aligns better with genuine enhancement in cortical engagement and information processing. Key limitations in this study are related to the nature of an open-label study design and sample size. Additionally, as pilot data, the correlation analysis in this study is exploratory, and the results should be interpreted with caution. This pattern strengthens the interpretation that the observed clinical and cognitive improvements are unlikely to stem from placebo effects, and more plausibly reflect true neurophysiological modulation.

Conclusion

This prospective pilot study provides preliminary evidence that TPS is a safe, well-tolerated, and potentially effective neuromodulatory treatment for Parkinson's disease. Improvements were consistent and clinically meaningful across motor, cognitive, and non-motor domains and were accompanied by EEG biomarkers indicative of enhanced neuroplasticity, including significant increases in theta/alpha and theta/beta ratios. Notably, baseline theta/beta ratios predicted treatment response, suggesting their potential as biomarkers for patient selection and personalized intervention strategies. Furthermore, the EEG signatures (e.g., increased alpha power or frontal alpha asymmetry) suggesting reduced placebo effect indicate that TPS effects reflect genuine cortical modulation rather than expectancy. This pilot study provided interesting, preliminary, and hypothesis-generating findings that justify further investigation of TPS in larger, sham-controlled trials and support the inclusion of EEG biomarkers to elucidate the mechanisms of action and optimize treatment targeting.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00415-025-13558-3.

Acknowledgements The authors are grateful to Dr. Markus Böbel and Dr. Henning Lohse-Busch, who contributed to the design of the intervention protocol and with useful recommendations using their own experience with TPS.

Author contributions Conceptualization: F.F., D.H., R.S. Funding acquisition: F.F., D.H., R.S. Methodology: F.F., D.H., R.S., A.G., L.C. Project administration: F.F., A.G., L.C. Data Curation: F.F., A.G., L.C.; investigation: F.F., A.G., L.C., H.-J.Y.; formal analysis: F.F., A.G., L.C. Supervision: FF. Writing—original draft: A.G., L.C., H.-J.Y., E.F.B., J.V.R., F.F. Writing—review and editing: A.G., L.C., H.-J.Y., E.F.B., J.V.R.; D.H., R.S., F.F.

Funding This study was funded by STORZ MEDICAL AG.

Data availability statement The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Conflicts of interest This study was funded by STORZ MEDICAL AG. Authors D.H-R. and R.S. are employees of STORZ MEDICAL AG. The other authors declare they have no financial interests.

Ethical standard statement The study was conducted at the Neuromodulation Center, Spaulding Rehabilitation Hospital, Mass General Brigham and was approved by the institutional review board. All participants provided informed consent according to the Declaration of Helsinki.

References

1. Luo Y, Qiao L, Li M, Wen X, Zhang W, Li X (2024) Global, regional, national epidemiology and trends of Parkinson's disease from 1990 to 2021: findings from the Global Burden of Disease Study 2021. Front Aging Neurosci 16:1498756. https://doi.org/10.3389/fnagi.2024.1498756
2. Ayuso P, Jiménez-Jiménez FJ, Gómez-Tabales J, Alonso-Navarro H, García-Martín E, Agúndez JAG (2023) An update on the pharmacogenetic considerations when prescribing dopamine receptor agonists for Parkinson's disease. Expert Opin Drug Metab Toxicol 19(7):447–460. https://doi.org/10.1080/17425255.2023.2249404
3. Murakami H, Shiraishi T, Umehara T, Omoto S, Iguchi Y (2023) Recent advances in drug therapy for Parkinson's disease (in eng). Intern Med 62(1):33–42. https://doi.org/10.2169/internalmedicine.8940-21
4. Pardo-Moreno T et al (2023) Current treatments and new, tentative therapies for Parkinson's disease. Pharmaceutics 15(3):770 (**online**)
5. Seppi K et al (2019) Update on treatments for nonmotor symptoms of Parkinson's disease-an evidence-based medicine review. Mov Disord 34(2):180–198. https://doi.org/10.1002/mds.27602
6. Benabid AL, Pollak P, Louveau A, Henry S, de Rougemont J (1987) Combined (thalamotomy and stimulation) stereotactic surgery of the VIM thalamic nucleus for bilateral Parkinson disease. Appl Neurophysiol 50(1–6):344–346. https://doi.org/10.1159/000100803
7. Lee JM, Pak K (2023) Comparison of UPDRS III score between young and late onset Parkinson disease after deep brain stimulation: a meta-analysis. Medicine (Baltimore) 102(44):e35861. https://doi.org/10.1097/md.0000000000035861
8. Zarate-Calderon C, Castillo-Rangel C, Viveros-Martínez I, Castro-Castro E, García LI, Marín G (2025) Risk of cerebrovascular events in deep brain stimulation for Parkinson's disease focused on STN and GPi: systematic review and meta-analysis. Brain Sci. https://doi.org/10.3390/brainsci15040413
9. Pomes MV et al (2025) Psychiatric outcomes of subthalamic nucleus deep brain stimulation: a systematic review of short- and long-term effects. Brain Sci. https://doi.org/10.3390/brainsci15060566
10. Xia S et al (2025) Non-invasive brain stimulation combined with exercise on gait in patients with Parkinson's disease: a systematic review and meta-analysis. NeuroRehabilitation 56(3):259–273. https://doi.org/10.1177/10538135251320263
11. Qiu Y et al (2023) Motor function improvement and acceptability of non-invasive brain stimulation in patients with Parkinson's disease: a Bayesian network analysis (in eng). Front Neurosci 17:1212640. https://doi.org/10.3389/fnins.2023.1212640
12. Moshayedi AJ, Mokhtari T, Emadi Andani M (2024) Brain stimulation techniques in research and clinical practice: a comprehensive review of applications and therapeutic potential in Parkinson's disease. Brain Sci. https://doi.org/10.3390/brainsci15010020
13. Cury RG, Pavese N, Aziz TZ, Krauss JK, Moro E, S. the Neuromodulation of Gait Study Group from Movement Disorders (2022) Gaps and roadmap of novel neuromodulation targets for treatment of gait in Parkinson's disease. npj Parkinson's Dis 8(1):8. https://doi.org/10.1038/s41531-021-00276-6
14. Giustiniani A, Maistrello L, Mologni V, Danesin L, Burgio F (2025) TMS and tDCS as potential tools for the treatment of cognitive deficits in Parkinson's disease: a meta-analysis. Neurol Sci 46(2):579–592. https://doi.org/10.1007/s10072-024-07778-0
15. Matt E et al (2022) First evidence of long-term effects of transcranial pulse stimulation (TPS) on the human brain. J Transl Med 20(1):26. https://doi.org/10.1186/s12967-021-03222-5
16. Beisteiner R, Lozano AM (2020) Transcranial ultrasound innovations ready for broad clinical application. Adv Sci 7(23):2002026. https://doi.org/10.1002/advs.202002026
17. Shinzato GT et al (2024) Non-invasive sound wave brain stimulation with transcranial pulse stimulation (TPS) improves neuropsychiatric symptoms in Alzheimer's disease. Brain Stimul 17(2):413–415. https://doi.org/10.1016/j.brs.2024.03.007
18. Lo HK et al (2024) Enhanced cognition and modulation of brain connectivity in mild neurocognitive disorder: the promise of Transcranial Pulse Stimulation. Biomedicines. https://doi.org/10.3390/biomedicines12092081
19. Beisteiner R et al (2020) Transcranial pulse stimulation with ultrasound in Alzheimer's disease-a new navigated focal brain therapy. Adv Sci (Weinh) 7(3):1902583. https://doi.org/10.1002/advs.201902583
20. Osou S et al (2024) Novel ultrasound neuromodulation therapy with transcranial pulse stimulation (TPS) in Parkinson's disease: a first retrospective analysis. J Neurol 271(3):1462–1468. https://doi.org/10.1007/s00415-023-12114-1
21. Manganotti P et al (2025) Effect of a single session of transcranial pulse stimulation (TPS) on resting tremor in patients with Parkinson's disease. Brain Res 1850:149405. https://doi.org/10.1016/j.brainres.2024.149405. (**in eng**)
22. Leung CHS, Simpson HD, Thyagarajan D (2025) The place of local field potentials in deep brain stimulation programming for Parkinson's disease: a review. Brain Sci. https://doi.org/10.3390/brainsci15020116. (**in eng**)
23. Gianlorenço AC et al (2025) Study protocol: investigating the effects of transcranial pulse stimulation in Parkinson's disease. Bioengineering 12(7):773 (**online**)
24. Postuma RB et al (2018) Validation of the MDS clinical diagnostic criteria for Parkinson's disease. Mov Disord 33(10):1601–1608. https://doi.org/10.1002/mds.27362
25. Matt E, Dorl G, Beisteiner R (2022) Transcranial pulse stimulation (TPS) improves depression in AD patients on state-of-the-art treatment. Alzheimers Dement (N Y) 8(1):e12245. https://doi.org/10.1002/trc2.12245
26. Lohse-Busch H, Marlinghaus E, Reime U, Möwis U (2014) Focused low-energy extracorporeal shock waves with distally symmetric polyneuropathy (DSPNP): a pilot study. NeuroRehabilitation 35(2):227–233. https://doi.org/10.3233/nre-141116
27. Lohse-Busch H (2021) Transcranial pulse stimulation (TPS) with focused extracorporeal shock waves. A new promising non invasive symptomatic treatment of Parkinson's disease: casuistics and feasibility Study. Preprint. https://doi.org/10.13140/RG.2.2.17406.72009
28. Weiner BJ et al (2017) Psychometric assessment of three newly developed implementation outcome measures. Implement Sci 12(1):108. https://doi.org/10.1186/s13012-017-0635-3
29. de Roborel Climens A, Findley A, Bury DP, Brady KJS, Reaney M, Gater A (2024) Development and content validation of the Patient's qualitative assessment of treatment-real-world (PQAT-RW): an instrument to evaluate benefits and disadvantages of treatments in real-world settings. Patient Relat Outcome Meas 15:255–269. https://doi.org/10.2147/prom.S468623
30. MurrinsMarques L et al (2025) PIPEMAT-RS: development and validation of a standardized MATLAB pipeline for resting-state EEG preprocessing (in eng). J Vis Exp. https://doi.org/10.3791/68350
31. Gianlorenco AC et al (2024) Understanding the effects of non-invasive transauricular vagus nerve stimulation on EEG and HRV. JoVE 203:e66309. https://doi.org/10.3791/66309
32. Lacerda GJM, Camargo L, Imamura M, Marques LM, Battistella L, Fregni F (2024) EEG oscillations as neuroplastic markers of neural compensation in spinal cord injury rehabilitation: the role of slow-frequency bands. Brain Sci 14(12):1229 (**online**)

33. Camargo L et al (2024) Evidence of bottom-up homeostatic modulation induced taVNS during emotional and Go/No-Go tasks. Exp Brain Res 242(9):2069–2081. https://doi.org/10.1007/s00221-024-06876-x
34. Marquez JO, Gonzalez-Gonzalez LF, Sosa W, Pacheco-Barrios K, Fregni F (2025) A salutogenic signature of the placebo effect in brain oscillations: a systematic review and meta-analysis (P4-4.007). Neurology 104(7_Supplement_1):5662. https://doi.org/10.1212/WNL.0000000000212510
35. Broelz EK, Enck P, Niess AM, Schneeweiss P, Wolf S, Weimer K (2019) The neurobiology of placebo effects in sports: EEG frontal alpha asymmetry increases in response to a placebo ergogenic aid. Sci Rep 9(1):2381. https://doi.org/10.1038/s41598-019-38828-9
36. Shulman LM, Gruber-Baldini AL, Anderson KE, Fishman PS, Reich SG, Weiner WJ (2010) The clinically important difference on the unified Parkinson's disease rating scale. Arch Neurol 67(1):64–70. https://doi.org/10.1001/archneurol.2009.295
37. Hauser RA, Auinger P (2011) Determination of minimal clinically important change in early and advanced Parkinson's disease. Mov Disord 26(5):813–818. https://doi.org/10.1002/mds.23638
38. Martinez-Martin P et al (2009) International study on the psychometric attributes of the non-motor symptoms scale in Parkinson disease (in eng). Neurology 73(19):1584–1591. https://doi.org/10.1212/WNL.0b013e3181c0d416
39. Carod-Artal FJ, Martínez-Martin P, Kummer W, Ribeiro Lda S (2008) Psychometric attributes of the SCOPA-COG Brazilian version (in eng). Mov Disord 23(1):81–87. https://doi.org/10.1002/mds.21769
40. Horváth K et al (2015) Minimal clinically important difference on Parkinson's disease sleep scale 2nd version. Parkinsons Dis 2015:970534. https://doi.org/10.1155/2015/970534
41. Xie CL, Shao B, Chen J, Zhou Y, Lin SY, Wang WW (2016) Effects of neurostimulation for advanced Parkinson's disease patients on motor symptoms: a multiple-treatments meta-analysas of randomized controlled trials (in eng). Sci Rep 6:25285. https://doi.org/10.1038/srep25285
42. Eghlidos Z, Rahimian Z, Vadiee G, Jahangiri S (2022) Effects of subthalamic deep brain stimulation on non-motor symptoms of Parkinson's disease: a meta-analysis. Acta Neurol Scand 146(2):115–125. https://doi.org/10.1111/ane.13652
43. Yahata K et al (2016) Low-energy extracorporeal shock wave therapy for promotion of vascular endothelial growth factor expression and angiogenesis and improvement of locomotor and sensory functions after spinal cord injury. J Neurosurg Spine 25(6):745–755. https://doi.org/10.3171/2016.4.Spine15923
44. d'Agostino MC, Craig K, Tibalt E, Respizzi S (2015) Shock wave as biological therapeutic tool: from mechanical stimulation to recovery and healing, through mechanotransduction. Int J Surg 24(B):147–153. https://doi.org/10.1016/j.ijsu.2015.11.030
45. Manganotti P et al (2025) Effects of Transcranial Pulse Stimulation (TPS) as a potential "add-on" intervention in patients with Parkinson's disease (in eng). Parkinsonism Relat Disord 142:108128. https://doi.org/10.1016/j.parkreldis.2025.108128
46. Haji S, Sako W, Murakami N, Osaki Y, Izumi Y (2024) Factors associated with a placebo effect in Parkinson's disease in clinical trials: a meta-analysis. J Neurol 271(9):5825–5837. https://doi.org/10.1007/s00415-024-12529-4
47. Fregni F et al (2006) Immediate placebo effect in Parkinson's disease—is the subjective relief accompanied by objective improvement? (in eng). Eur Neurol 56(4):222–229. https://doi.org/10.1159/000096490
48. Duan W, Chen X, Wang Y-J, Zhao W, Yuan H, Lei X (2021) Reproducibility of power spectrum, functional connectivity and network construction in resting-state EEG. J Neurosc Methods 348:108985. https://doi.org/10.1016/j.jneumeth.2020.108985
49. Herweg NA, Solomon EA, Kahana MJ (2020) Theta oscillations in human memory. Trends Cogn Sci 24(3):208–227. https://doi.org/10.1016/j.tics.2019.12.006. (**in eng**)
50. Hölscher C, Anwyl R, Rowan MJ (1997) Stimulation on the positive phase of hippocampal theta rhythm induces long-term potentiation that can be depotentiated by stimulation on the negative phase in area CA1 in vivo (in eng). J Neurosci 17(16):6470–6477. https://doi.org/10.1523/jneurosci.17-16-06470.1997
51. Huerta PT, Lisman JE (1995) Bidirectional synaptic plasticity induced by a single burst during cholinergic theta oscillation in CA1 in vitro in eng. Neuron 15(5):1053–1063. https://doi.org/10.1016/0896-6273(95)90094-2
52. Pacheco-Barrios K et al (2024) Brain compensatory mechanisms in depression and memory complaints in fibromyalgia: the role of theta oscillatory activity. Pain Med 25(8):514–522. https://doi.org/10.1093/pm/pnae030. (**in eng**)
53. Lacerda GJM, Costa V, Camargo L, Battistella LR, Imamura M, Fregni F (2025) Neurophysiological markers of adaptation and compensation following lower limb amputation: an analysis of EEG oscillations and clinical predictors from the DEFINE cohort study (in eng). Neurol Int. https://doi.org/10.3390/neurolint17020021
54. Ye Z, Heldmann M, Herrmann L, Brüggemann N, Münte TF (2022) Altered alpha and theta oscillations correlate with sequential working memory in Parkinson's disease (in eng). Brain Commun 4(3):096. https://doi.org/10.1093/braincomms/fcac096
55. Lacerda GJM, Pacheco-Barrios K, Barbosa SP, Marques LM, Battistella L, Fregni F (2024) A neural signature for brain compensation in stroke with EEG and TMS: insights from the DEFINE cohort study. Neurophysiol Clin 54(5):102985. https://doi.org/10.1016/j.neucli.2024.102985
56. Chang J, Choi Y (2023) Depression diagnosis based on electroencephalography power ratios. Brain Behav 13(8):e3173. https://doi.org/10.1002/brb3.3173. (**in eng**)
57. Lacerda GJM, Silva FMQ, Pacheco-Barrios K, Battistella LR, Fregni F (2024) Adaptive compensatory neurophysiological biomarkers of motor recovery post-stroke: electroencephalography and transcranial magnetic stimulation insights from the DEFINE cohort study (in eng). Brain Sci. https://doi.org/10.3390/brainsci14121257
58. Silva-Passadouro B et al (2022) Frontal alpha asymmetry: a potential biomarker of approach-withdrawal motivation towards pain (in English). Front Pain Res. https://doi.org/10.3389/fpain.2022.962722